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N-Sulfonylamidines. Part IV [1]. Intramolecular Cyclization of N-Sulfonylamidines of 2-Oxoacids: a new Synthesis of 3-Aminoisothiazole S,S-dioxides.

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Key Words: N-Sulfonylamidines/ 3-Amino-isothiazole S,S-dioxides/ Intramolecular Cyclization/ Isothiazoline S,S-dioxides/ Configuration/

Abstract: *N-alkylsulfonylamidines of α-ketoacids 3 bearing both a carbonyl group and at least one H-atom near to the SO_2 group give easily an intramolecular ring-closure reaction by action of potassium t-butoxide producing the 3-amino-4,5-dihydro-4-hydroxy-isothiazole S,S-dioxides 4. Compounds 4 are transformed by thionyl chloride into the corresponding chloro-derivatives 5 which in turn are dehydrochlorinated by potassium carbonate to substituted 3-amino-isothiazole S,S-dioxides 6.*

For several years we have been actively interested in the synthetic exploitation of N-sulfonylamidines[2-4]. More particularly, we have shown that a N-sulfonylamidine having at least an hydrogen atom α to the SO_2 group reacts with strong bases producing a carbanionic intermediate which undergoes an intramolecular cyclization affording enamines, thiazete-S,S-dioxides and β-sulfonylenamines through a thiazetidine intermediate[1]. This useful result prompted us to investigate other classes of N-sulfonylamidines with intrinsic possibility of intramolecular cyclization. Our results with N-alkylsulfonylamidines of α-oxoacids are reported in the present paper.

Amidines. As shown in Scheme 1 the amidines **3** were obtained by reaction of sulfonylazides **1** with enamines **2**. Azides **1** are known compounds and were prepared according to conventional procedures[5]. The hitherto unknown enamines **2b,c** were prepared as described for **2a**[6], i.e. by reaction of diethylamine with the corresponding 1-aryl-3-phenyl-2,3-dibromo-1-propanones, whereas compounds **2d-f** were obtained according to the method which has been reported for the diphenyl analogue of **2d**[6], i.e. by addition of the appropriate

amine to the corresponding 1-aryl-3-phenyl-2-bromoprop-2-en-1-one and base catalyzed elimination of hydrogen bromide. The reaction of the azides **1** with the enamines **2** was performed in boiling ethanol. Amidines **3** are produced through 1,3-dipolar cycloaddition of the azide to the enamine double bond. The intermediate v-triazoline adducts are quite unstable, as observed in analogous cases[8], and cannot be isolated. Instead, they spontaneously undergo cycloreversion with elimination of phenyldiazomethane producing compounds **3**.

Scheme 1

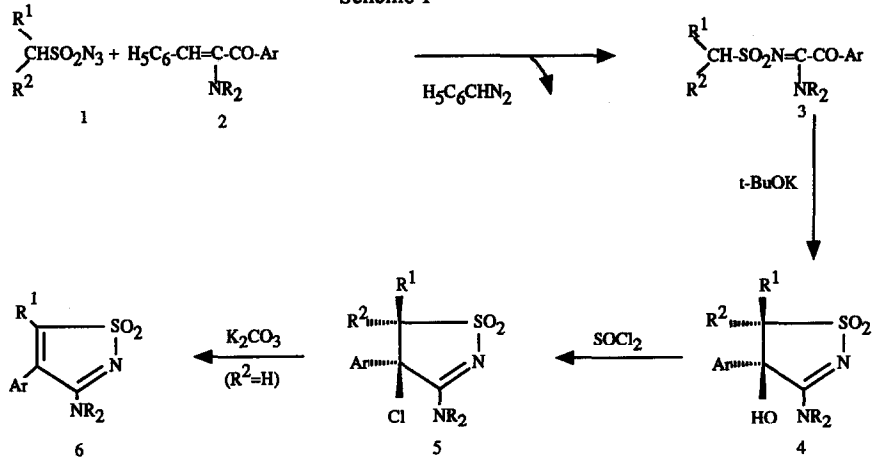
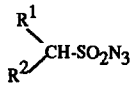
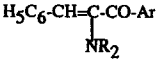


Table 1



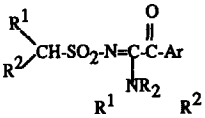
1	R^1	R^2
a	C_6H_5	H
b	o-NO_2-C_6H_4	H
c	H	H
d	CH_3	H
e	CH_3	CH_3

Table 2



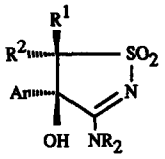
2	Ar	NR_2
a	C_6H_5	diethylamino
b	p-CH_3-C_6H_4	diethylamino
c	p-CH_3O-C_6H_4	diethylamino
d	p-CH_3-C_6H_4	morpholino
e	p-CH_3-C_6H_4	pyrrolidino
f	p-CH_3O-C_6H_4	morpholino

Table 3



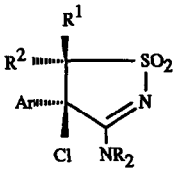
3	Ar	R^1	R^2	NR_2
a	C_6H_5	C_6H_5	H	diethylamino
b	p-CH_3-C_6H_4	C_6H_5	H	diethylamino
c	p-CH_3O-C_6H_4	C_6H_5	H	diethylamino
d	C_6H_5	o-NO_2-C_6H_4	H	diethylamino
e	C_6H_5	H	H	diethylamino
f	p-CH_3-C_6H_4	H	CH_3	morpholino
g	C_6H_5	H	CH_3	diethylamino
h	p-CH_3-C_6H_4	H	H	diethylamino
i	p-CH_3-C_6H_4	H	H	morpholino
l	p-CH_3O-C_6H_4	H	H	diethylamino
m	C_6H_5	CH_3	CH_3	diethylamino
n	p-CH_3-C_6H_4	H	C_6H_5	morpholino
o	p-CH_3O-C_6H_4	H	H	pyrrolidino
p	p-CH_3O-C_6H_4	H	H	morpholino

Table 4



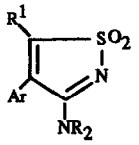
4	Ar	R^1	R^2	NR_2
a	C_6H_5	C_6H_5	H	diethylamino
b	C_6H_5	H	C_6H_5	diethylamino
c	p-CH_3-C_6H_4	C_6H_5	H	diethylamino
d	p-CH_3-C_6H_4	H	C_6H_5	diethylamino
e	p-CH_3O-C_6H_4	C_6H_5	H	diethylamino
f	p-CH_3O-C_6H_4	H	C_6H_5	diethylamino
g	C_6H_5	o-NO_2-C_6H_4	H	diethylamino
h	C_6H_5	H	o-NO_2-C_6H_4	diethylamino
i	C_6H_5	H	H	diethylamino
l	p-CH_3-C_6H_4	H	CH_3	morpholino
m	p-CH_3-C_6H_4	CH_3	H	morpholino
n	C_6H_5	H	CH_3	diethylamino
o	C_6H_5	CH_3	H	diethylamino
p	p-CH_3-C_6H_4	H	H	diethylamino
q	p-CH_3-C_6H_4	H	H	morpholino
r	p-CH_3O-C_6H_4	H	H	diethylamino
s	C_6H_5	CH_3	CH_3	diethylamino
t	p-CH_3-C_6H_4	C_6H_5	H	morpholino
u	p-CH_3O-C_6H_4	H	C_6H_5	morpholino
v	p-CH_3O-C_6H_4	H	H	pyrrolidino
z	p-CH_3O-C_6H_4	H	H	morpholino

Table 5



5	Ar	R^1	R^2	NR_2
a	p-CH_3O-C_6H_4	C_6H_5	H	diethylamino
b	p-CH_3O-C_6H_4	H	C_6H_5	diethylamino
c	C_6H_5	H	H	diethylamino
d	p-CH_3-C_6H_4	H	H	diethylamino
e	p-CH_3-C_6H_4	H	H	morpholino
f	p-CH_3O-C_6H_4	H H	H	diethylamino
g	p-CH_3-C_6H_4	H	C_6H_5	morpholino
h	p-CH_3-C_6H_4	C_6H_5	H	morpholino
i	p-CH_3O-C_6H_4	H	H	pyrrolidino
l	p-CH_3O-C_6H_4	H	H	morpholino

Table 6



6	Ar	R^1	NR_2
a	p-CH_3O-C_6H_4	C_6H_5	diethylamino
b	p-CH_3-C_6H_4	H	diethylamino
c	p-CH_3O-C_6H_4	H	diethylamino
d	p-CH_3-C_6H_4	C_6H_5	morpholino
e	p-CH_3O-C_6H_4	H	pyrrolidino
f	p-CH_3O-C_6H_4	H	morpholino

Isothiazolines 4,5 and Isothiazoles 6. Compounds **3** represent a new class of N-sulfonylamidine, containing at once, an acidic hydrogen α to the SO_2 group, and a carbonyl group directly bonded to the amidine carbon. Owing to these structural features they readily cyclized when treated with alkaline alkoxides. The best results were obtained by using potassium t-butoxide.

As a rule the ring-closure products, i.e. the corresponding 3-amino-4-hydroxy-4,5-dihydroisothiazoles **4** (Scheme 1), were obtained in good yields. Clearly, products **4** are formed by deprotonation of the starting compounds α to the SO_2 group and intramolecular attack of the resulting carbanion at the CO group.

On reaction with excess of thionyl chloride at reflux, compounds **4** smoothly produced the corresponding chloro-derivatives **5** in good yields by substitution of the hydroxy group. When R^2 corresponds to hydrogen atom, compounds **5** can readily be dehydrohalogenated to the 3-aminoisothiazole S,S-dioxide derivatives **6**. This reaction was best performed by potassium carbonate in acetone; triethylamine gave poor results. Other bases, particularly nucleophilic bases as ammonia and primary and secondary amines, gave complex reaction mixtures which are currently under study.

A thermal elimination was observed in a variable temperature ^{1}H-NMR experiment. However, this way to transform **5** to **6** is not suitable for practical purposes. Direct production of compounds **6** from the products **4** by dehydration failed to give acceptable results since the hydroxy compounds **4** appear to be resistant to some common dehydrating agents (e.g. P_2O_5, $ZnCl_2$, KOH, acetic anhydride, trace of mineral acids,treatment with bases and so on).

Conformation and configuration of isothiazoles. The structures of all products were confirmed by analytical and spectroscopic (IR, ^{1}H-NMR and MS) evidence. In compounds **4** and **5**, when R^1 is different from R^2, two diastereomeric products are to be expected. Indeed, in all cases a mixture of both diastereomers in a nearly 1 to 1 ratio was obtained. Most of them were separated in a pure condition and their configuration was established by ^{1}H-NMR. For the sake of clarity only the pair **4a** and **4b** will be discussed in detail in the following since the results can straightforwardly be extended to all cases. As shown in Table 8 the ^{1}H-NMR spectrum ($CDCl_3$) of **4b** is characterized by a signal (singlet) at 5.2 δ corresponding to H-5 and another singlet at 5.5 δ associated with the OH group. The corresponding values for **4a** are 4.6 δ and 3.5 δ respectively. From the observed chemical shifts a configurational assignment can be inferred taking into account the shielding effect which should be exerted by the aromatic rings on cis substituents on C-4. According to this reasoning the **4R*5S*** and **4R*5R*** configurations can be assigned to **4b** and **4a**, respectively. To confirm this assignment a NOESY spectrum was recorded, showing a clear correlation between the H and OH groups only for compound **4a** in which they are cis. On analogous evidence the

configuration was assigned to the other diastereomeric pairs. A similar situation was observed in the case of compounds **5**. For example, in **5b** the H-5 resonance is found downfields with respect to **5a**. In agreement with this the NOESY spectrum of **5a** evidences a correlation between H-5 and the aromatic hydrogens of the 4-methoxyphenyl group on C-4, which is absent in **5b**. A striking feature of the ^{1}H-NMR spectrum of all compounds **4,5** and **6** is the great complexity of the signals associated with the morpholino, pyrrolidino and diethylamino groups bonded to C-3, showing the magnetic non-equivalence of chemically identical hydrogens. This points to a rotational barrier about the C-N bond which can be explained by an extensive conjugation of the amidine system. Variable temperature ^{1}H-NMR experiments which evidenced the coalescence of the signals at about 80-90° C. By applying the Arrhenius equation rotational barriers of about 17-18 Kcal/mol were calculated for compounds **4,5** and **6** respectively, which is in fair agreement with structurally similar cases[9,10,11].

EXPERIMENTAL

IR spectra were recorded on a Pye Unicam SP3-200 S Philips spectrophotometer. ^{1}H-NMR spectra (tetramethylsilane as internal standard, $CDCl_3$ as solvent or DMSO in variable temperature experiments): Bruker AC 200, Bruker AC 300 equipped with a VT 1000 Unit to perform variable temperature experiments. TLC: ready-to-use silica gel plates with cyclohexane/ethyl acetate or diethyl ether as eluant. Column chromatography: silica gel with the eluant indicated. Melting points: not corrected. M.S.: Varian Mat INCOS 50 instrument.

*Sulfonyl azides **1a-e**.* Products **1a,b,c,d** are known compounds [1,12,13]. Sulfonyl azide **1e** was prepared from the corresponding sulfonyl chloride[14] according to a published procedure[5].

1e: $C_7H_6N_4O_4S$ (272); Yield: 79%; Calcd.: C 34.56% H 2.52% N 22.88% Found: C 34.72% H 2.49% N 23.14%. M.p.: 97°.

*Enamines **2a-f**.* Enamine **2a** is known compound[6]. Enamines **2b,c,d,e,f** were prepared according to published procedures[6,7].

2b: $C_{20}H_{23}NO$; Calcd.293 Found 293 (MS); ^{1}H-NMR ($CDCl_3$): 5.6 δ (CH=C-N).

2c: $C_{20}H_{23}NO_2$; Calcd.309 Found 309 (MS); ^{1}H-NMR ($CDCl_3$): 5.6 δ (CH=C-N).

2d: $C_{20}H_{21}NO_2$; Calcd.307 Found 307 (MS); ^{1}H-NMR ($CDCl_3$): 5.7 δ (CH=C-N).

2e: $C_{21}H_{23}NO$; Calcd.305 Found 305 (MS); ^{1}H-NMR ($CDCl_3$): 5.6 δ (CH=C-N).

2f: $C_{20}H_{21}NO_3$; Calcd.323 Found 323 (MS); ^{1}H-NMR ($CDCl_3$): 5.8 δ (CH=C-N).

*General procedure for the preparation of N-sulfonylamidines **3 a-p**.* A solution of azide **1** in ethanol

was dropped into a solution of enamine **2** in the same solvent under stirring at room temperature. After the addition the mixture was refluxed until the reactants were no longer detectable by TLC (about 8 hours). The solvent was evaporated and the residue was crystallized from diethyl ether. In other cases chromatographic purification of the reaction mixture (eluant cyclohexane/ethyl acetate 4:6) was performed. Analytical and spectroscopic data are listed in Table 7.

General procedure for the preparation of 3-amino-4,5-dihydro-4-hydroxy-isothiazole S,S-dioxides **4a-z.** To a stirred solution of the appropriate N-sulfonylamidine **3** (1 mol.) in anhydrous THF, under nitrogen, an equimolecular amount of potassium t-butoxide was added. Stirring was continued for about 6 hours and the end of the reaction was checked by TLC (cyclohexane/ethyl acetate 4:6). The reaction mixture was evaporated and neutralized with a 10% HCl solution, and the product was extracted into CH_2Cl_2 and washed twice with water. The organic layer was separated, dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. Product **4** was crystallized from diethyl ether. The pairs of diastereomers **4a,b**; **4c,d**; **4e,f**; **4n,o**; **4t,u**; were separated by flash chromatography (eluant diethyl ether/petroleum ether 1:1). From the mixture **4n,o** only **4o** could be obtained in a pure form. **4n** was always obtained in mixture with **4o** and attempts to purify it failed. Analytical and spectroscopic data are listed in Table 8.

General procedure for the preparation of 3-amino-4-chloro-4,5-dihydroisothiazole S,S-dioxides **5a-l.** Product **4** was refluxed in $SOCl_2$ until disappearance of the reactant (TLC). The solvent was then distilled off under reduced pressure; the residue was neutralized with 10% $NaHCO_3$ solution, extracted into CH_2Cl_2 and washed with water. The organic layer was separated, dried over Na_2SO_4 and filtered; the solvent was evaporated under reduced pressure,and the residue was crystallized from diethyl ether. The pairs of diastereomers **5a,b**; **5g,h**; were separated as described above by flash chromatography (eluant diethyl ether/petroleum ether 1:1). Analytical and spectroscopic data are listed in Table 9.

General procedure for preparation of 3-amino-isothiazole S,S-dioxides **6.** To a solution of **5** in anydrous acetone an equimolecular amount of solid K_2CO_3 was added under vigorous stirring. The suspension was refluxed until complete disappearance of the reactant (TLC eluant cyclohexane/ethyl acetate 4:6, about 48 hours). The solvent was then evaporated under reduced pressure and the residue was taken up in 10% HCl solution, extracted with CH_2Cl_2 and washed twice with water. The organic layer was separated, dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The residue was crystallized from diethyl ether. Analytical and spectroscopic data are listed in Table 10.

Table 7
Analytical and Spectroscopic data for compounds 3

Prod.	Yield %	M.p. °C	M.w.	Calcd.(Found) C	H	N	^{1}H-NMR
a	70	154	328	63.7 (64.0)	6.1 (6.2)	7.8 (7.7)	0.9 (t, J=7Hz, 3H, CH_3); 1.2 (t, J=7Hz, 3H, CH_3,); 3.3-3.8 (m, 4H, CH_2); 4.2 (s, 2H, CH_2); 7.1-7.7 (m, 10H Aryl H).
b	58	106-108	342	64.5 (64.4)	6.4 (6.4)	7.5 (7.6)	0.9 (t, J=7Hz, 3H, CH_3); 1.2 (t, J=7Hz, 3H, CH_3); 2.3 (s, 3H, CH_3); 3.0 (q, J= 7Hz, 2H, CH_2); 3.3-3.6 (m, 2H, CH_2); 4.2 (s, 2H, CH_2); 7.2 (AB system , 2H, J=8Hz, J=8Hz, Aryl H); 7.3 (s, 5H, Aryl H); 7.6 (AB system, J=8Hz, 2H, Aryl H).
c	53	120	358	61.8 (61.5)	6.2 (6.1)	7.2 (7.1)	0.9 (t, J=7Hz, 3H, CH_3); 1.1 (t, J=7Hz, 3H, CH_3); 3.1 (q, J=7Hz, 2H,CH_2); 3.3-3.7 (m, 2H); 3.8 (s, 3H, OCH_3); 4.2 (s, 2H, CH_2); 6.8 (AB system, J=8Hz, 2H, Aryl H); 7.3 (s, 5H, Aryl H); 7.6 (AB system, J=8Hz, 2H, Aryl H).
d	50	143	403	56.6 (56.3)	5.2 (5.1)	10.4 (10.4)	1.0 (t, J=7Hz, 3H, CH_3); 1.3 (t, J=7Hz, 3H, CH_3); 3.1 (q, J=7Hz, 2H, CH_2); 3.4-3.8 (m, 4H, CH_2); 4.2 (s, 2H, CH_2); 7.3-8.0 (m, 9H, Aryl H).
e	60	80	282	55.3 (55.6)	6.4 (6.5)	9.9 (9.8)	0.9-1.3 (m, 6H, CH_3); 2.8-3.5 (m, 4H, CH_2); 3.7 (s, 3H, CH_3); 7.2-8.0 (m, 5H, Aryl H).
f	70	119	324	55.5 (55.6)	6.2 (6.2)	8.6 (8.6)	1.3 (t, J=8Hz, 3H, CH_3); 2.4 (s, 3H, CH_3); 3.0 (q, J=8Hz, 2H, CH_2); 3.2 (m, 2H, CH_2 morph.); 3.6 (m, 2H, CH_2 morph.); 3.8-4.0 (m, 4H, $CH_2O_{morph.}$); 7.2 (AB system, J=8Hz, 2H, Aryl H); 7.8 (AB system, J=8Hz, 2H, Aryl H).
g	60	100-101	296	56.7 (56.6)	6.7 (6.6)	9.5 (9.5)	0.9-1.5 (m, 9H, $\underline{CH_3}CH_2N + \underline{CH_3}CH_2S$); 2.9-3.9 (m, 6H, $CH_3\underline{CH_2}N + CH_3\underline{CH_2}S$); 7.3-8 (m, 5H, Aryl H).
h	70	123	296	56.7 (56.6)	6.7 (6.6)	9.4 (9.4)	1.1 (t, J=7Hz, 3H, CH_3); 1.3 (t, J=7Hz, 3H, CH_3); 2.4 (s, 3H, CH_3); 2.9 (s, 3H, CH_3SO_2); 3.25 (q, J=7Hz, 2H, CH_2); 3.2-3.9 (m, 2H, CH_2); 7.3 (AB system, J= 8Hz, 2H, Aryl H); 7.8 (AB system, J=8Hz, 2H, Aryl H).
i	65	160	310	54.2 (54.0)	5.8 (5.7)	9.0 (8.9)	2.4 (s, 3H, CH_3); 3.0 (s, 3H, CH_3SO_2) ; 3.1-4.0 (m, 8H, $CH_{2morph.}$); 7.3 (AB system J=8Hz, 2H, Aryl H); 7.9 (AB system, J=8Hz, 2H, Aryl H).
l	55	116	312	53.8 (53.5)	6.4 (6.4)	9.0 (8.9)	1.0 (t, J=7Hz, 3H, CH_3); 1.2 (t, J=7Hz, 3H, CH_3); 2.9 (s, 3H, CH_3SO_2); 3.1 (q, J= 7Hz, 2H, CH_2); 3.3-3.8 (m, 2H, CH_2); 3.9 (s, 3H, CH_3O); 6.9 (AB system, J=8Hz, 2H, Aryl H); 7.9 (AB system, J=8Hz, 2H, Aryl H).
m	70	95	310	58.1 (57.8)	6.4 (7.3)	9.0 (8.8)	0.9-1.1 (m, 12H,$(\underline{CH_3})_2CH + \underline{CH_3}CH_2N$); 2.9-3.9 (m, 5H, $(CH_3)_2\underline{CH} + CH_3\underline{CH_2}N$); 7.3-8.0 (m, 5H,Aryl H).
n	70	168	402	62.2 (62.0)	5.7 (5.7)	7.2 (7.2)	2.5 (s, 3H, CH_3); 3.3- 3.4 (m, 2H, CH_2 morph.); 3.5-3.6 (m, 2H, CH_2 morph.);3.6-3.8 (m, 4H, $CH_2O_{morph.}$); 4.4 (s, 2H, CH_2); 7.2 (AB system, J=8Hz, 2H, Aryl H); 7.5 (AB system, J=8Hz, 2H, Aryl H).
o	73	200	324	55.5 (55.4)	6.2 (5.9)	8.6 (8.4)	1.4-1.9 (m, 6H, CH_2 pyrrol.); 3.0 (s, 3H, CH_3SO_2) ; 3.2-3.3 (m, 2H, CH_2 pyrrol.); 3.7-3.8 (m, 2H, CH_2 pyrrol.); 3.8 (s, 3H, CH_3O); 6.9 (AB system, J=8Hz, 2H, Aryl H); 7.9 (AB system, J=8Hz, 2H, Aryl H).
p	75	165	326	51.5 (51.3)	5.5 (5.6)	8.6 (8.5)	3.0 (s, 3H, CH_3SO_2); 3.2-3.4 (m, 2H, CH_2 morph.); 3.5-3.6 (m, 2H, CH_2 morph.); 3.8-3.9 (m, 4H, $CH_{2morph.}$); 3.9 (s, 3H, CH_3O); 7.0 (AB system, J=8Hz, 2H, Aryl H); 7.9 (AB system, J=8Hz, 2H, Aryl H).

Table 8

Analytical and Spectroscopic data for compounds 4

Prod.	Yield %	M.p. °C	M.w.	Calcd.(Found) C	H	N	^{1}H-NMR
a	70[a]	227	328	63.7 (63.5)	6.1 (6.1)	7.8 (7.8)	0.7 (t, J=7Hz, 3H, CH_3); 1.3 (t, J=7Hz, 3H, CH_3,); 3.0-3.2 (m, 2H, CH_2); 3.3 (s, 1H, OH); 3.4-3.6(m, 1H, CH_2); 3.6-3.7(m, 1H, CH_2); 4.6 (s, 1H, CH-SO_2); 7.1-7.4 (m, 10H, Aryl H).
b		240	328	63.7 (63.6)	6.1 (6.2)	7.8 (7.9)	0.9 (t, J=7Hz, 3H, CH_3); 1.2 (t, J=7Hz, 3H, CH_3); 2.8-2.9 (m, 1H, CH_2); 3.4-3.3 (m, 2H, CH_2); 3.6-3.7 (m, 1H, CH_2); 5.2 (s, 1H, CH-SO_2); 5.3 (s, 1H, OH); 7.1 -7.4 (m, 10H, Aryl H).
c	60[a]	166	342	64.5 (64.3)	6.4 (6.4)	7.3 (7.4)	0.8 (t, J=7Hz, 3H, CH_3); 1.3 (t, J=7Hz, 3H, CH_3); 2.4 (s, 3H, CH_3); 3.2 (q, J=7Hz, 2H, CH_2); 3.3-3.5 (m, 1H, CH_2); 3.7-3.9 (m, 1H, CH_2); 4.6 (s, 1H, CH-SO_2); 7.1-7.4 (m, 9H, Aryl H).
d		180	342	64.5 (64.4)	6.4 (6.5)	7.3 (7.5)	0.9 (t, J=7Hz, 3H, CH_3); 1.2 (t, J=7Hz, 3H, CH_3); 2.3 (s, 3H, CH_3); 3.1 (m, 2H, CH_2); 3.2-3.6 (m, 2H, CH_2); 5.2 (s, 1H, CH-SO_2); 5.5 (s, 1H, OH); 7.1 (m, 5H, Aryl H); 7.2-7.4 (m, 5H, Aryl H).
e	55[a]	160	358	61.8 (61.5)	6.2 (6.1)	7.2 (7.1)	0.8 (t, J=7Hz, 3H, CH_3); 1.4 (t, J=7Hz, 3H, CH_3); 3.1(q, J=7Hz, 2H, CH_2); 3.3 (s, 1H, OH); 3.4-3.6(m, H, CH_2); 3.7-3.9 (m, 1H, CH_2); 3.8 (s, 3H, CH_3O); 4.6 (s, 1H, CH-SO_2); 6.9-7.4 (m, 9H, Aryl H).
f		185	358	61.8 (61.8)	6.2 (6.1)	7.2 (7.1)	0.9 (t, J=7Hz, 3H, CH_3); 1.2 (t, J=7Hz, 3H, CH_3); 2.9-3.6 (m, 4H, CH_2); 3.7 (s, 3H, CH_3O); 5.2 (s, 1H, CH-SO_2); 5.3 (s, 1H, OH); 6.7 (AB system, J=8Hz, 2H, Aryl H); 6.9-7.4 (m, 7H, Aryl H).
g + h[b]	57	/	403	56.6 (56.9)	5.2 (5.2)	10.4 (10.4)	0.6 (m, 6H, CH_3); 1.1 (m, 6H, CH_3); 3.1-3.6 (m, 11H, CH_2+CH-SO_2+OH); 6.8-8.3 (m, 19H, Aryl H+ OH).
i	30	164	282	55.3 (55.1)	6.4 (6.3)	9.9 (9.7)	0.8 (t, J=6.5Hz, 3H, CH_3); 1.3 (t, J=6.5Hz, 3H, CH_3); 3.3 (q, J=6.5 Hz, 2H, CH_2); 3.5 (q, J=6.5Hz, 2H CH_2); 3.6 (AB system, J=13Hz, 1H, CH-SO_2); 3.8 (s, 3H, CH_3O); 3.9 (AB system, J=13Hz, 1H, CH-SO_2); 5.5 (s, 1H, OH); 6.9 (AB system, J=8Hz, 2H, Aryl H); 7.4 (AB system, J=8Hz, 2H, Aryl H).
l + m[b]	40[a]	/	324	55.5 (55.2)	6.2 (6.3)	8.6 (8.6)	1.3 (d, J=8Hz, 6H, CH_3); 2.3 (s, 6H, CH_3); 2.8-4 (m, 19H, $CH_{2morph.}$+ CH-SO_2 + OH); 4.5 (s, 1H, OH); 7.0-7.3 (m, 8H, Aryl H).
n[c]	63[a]	/	296	56.7 (56.6)	6.7 (6.9)	9.4 (9.5)	0.8 -1.0 (m, 6H, $\underline{CH_3}CH_2$); 1.2-1.4 (m, 3H, $\underline{CH_3}CH$); 3.0-3.6 (m, 4H, CH_2); 3.9 (q, J=7Hz, 1H, $CH_3\underline{CH}$); 5.4 (s, 1H, OH); 7.2-7.4 (m, 5H, Aryl H).
o		164	296	56.7 (57.0)	6.7 (7.1)	9.4 (9.2)	0.6 (t, J=6.6Hz, 3H, CH_3); 1.2 (t, J=6.6Hz, 3H, CH_3); 1.2 (d, J=7Hz, 3H, $\underline{CH_3}CH$); 3.0-3.3 (m, 2H, CH_2); 3.4 (q, J=6.6Hz, 2H, CH_2); 3.6 (q, J=7Hz, 1H, $\underline{CH_3}CH$); 4.6 (s, 1H, OH); 7.3-7.4 (m, 5H, Aryl H).

Table 8 (continuation)

p	70	174	296	56.7 (57.0)	6.7 (7.1)	9.4 (9.2)	0.8 (t, J=7Hz, 3H, CH_3); 1.2 (t, J=7Hz, 3H, CH_3); 2.3 (s, 3H, CH_3); 3.3 (q, J=7Hz, 2H, CH_2); 3.3-3.5 (m, 2H, CH_2); 3.6 (AB system, J=15Hz, 1H, CH-SO_2); 3.9 (AB system, J=15Hz, 1H, CH-SO_2); 7.2 (AB system , J=8Hz, 2H, Aryl H); 7.4 (AB system, J=8Hz, 2H, Aryl H).
q	47	238	310	54.2 (54.0)	5.8 (5.7)	9.0 (9.0)	2.4 (s, 3H, CH_3); 3.1-3.8 (m, 8H, $CH_{2morph.}$); 3.6 (AB system, J=15Hz, 1H, CH-SO_2); 3.9 (AB system J=15Hz, 1H, CH-SO_2); 5.5 (s, 1H, OH); 7.2 (AB system, J=8Hz, 2H, Aryl H); 7.4 (AB system, J=8Hz, 2H, Aryl H).
r	78	177	312	53.8 (53.3)	6.4 (6.3)	9.0 (8.5)	0.8 (t, J=7Hz, 3H, CH_3); 1.2 (t, J=7Hz, 3H, CH_3); 3.2 (q, J=7Hz, 2H, CH_2); 3.4 (q, J=7Hz, 2H, CH_2); 3.6 AB system, J=15Hz, 1H, CH-SO_2); 3.7 (s, 3H, CH_3O); 3.9 (AB system, J=15Hz, 1H, CH-SO_2); 6.9 (AB system, J=8Hz, 2H, Aryl H); 7.4 (AB system, J=8Hz, 2H, Aryl H).
s	54	168	310	58.1 (58.2)	6.4 (7.3)	9.0 (9.0)	0.9 (t, J=7Hz, 3H, CH_3); 1.2 (t, J=7Hz, 3H, CH_3); 1.5 (s, 6H, CH_3C-SO_2); 2.9-3.5 (m, 2H, CH_2); 3.6 (s, 1H, OH); 3.7-3.9 (m, 2H, CH_2); 7.4 (m, 5H, Aryl H).
t	60 [a]	240	402	62.2 (62.0)	5.7 (5.6)	7.2 (7.0)	2.4 (s, 3H, CH_3); 3.0-3.4 (m, 4H, $CH_{2morph.}$); 3.5 (s, 1H, OH); 3.6-4.1 (m, 4H, $CH_{2morph.}$); 4.6 (s, 1H, CH-SO_2); 7.0-7.4 (m, 9H, Aryl H).
u		211	402	62.2 (62.0)	5.7 (5.7)	7.2 (7.0)	2.3 (s, 3H, CH_3); 3.0-4.0 (m, 8H, $CH_{2morph.}$); 5.2 (s, 1H, CH-SO_2); 5.5 (s, 1H, OH); 6.9-7.4 (m, 9H, Aryl H).
v	50	185	324	55.5 (55.9)	6.2 (6.6)	8.6 (8.2)	1.4-1.8 (m, 6H, $CH_{2pyrrol.}$); 3.1-3.5 (m, 4H, $CH_{2pyrrol.}$); 3.6 (AB system, J=14Hz, 1H, CH-SO_2); 3.7 (s, 1H, OH); 3.8 (s, 3H, CH_3O); 4.0 (AB system, J=14Hz, 1H, CH-SO_2); 6.8 (AB system, J=8Hz, 2H, Aryl H); 7.4 (AB system, J=8Hz, 2H, Aryl H).
z	68	138	326	51.5 (51.4)	5.5 (5.7)	8.6 (8.7)	3.2-3.4 (m, 3H, $CH_{2morph.}$); 3.5-3.8 (m, 5H, $CH_{2morph.}$); 3.8 (s, 3H, CH_3O); 3.7 (AB system, J=14Hz, 1H, CH-SO_2); 3.9 (AB system, J=14Hz, 1H, CH-SO_2); 5.4 (s, 1H, OH); 6.9 (AB system, J=8Hz, 2H, Aryl H); 7.4 (AB system, J=8Hz, 2H, Aryl H).

a) Total yield of the isolated mixture of the two diastereomers - b) not separated - c) only an impure sample was obtained without a definite m.p.

Table 9

Analytical and Spectroscopical data for compounds 5

Prod.	Yield %	M.p. °C	M.w.	Calcd.(Found) C	H	N	^{1}H-NMR
a	70 [a]	144	406.5	59.0 (59.0)	5.5 (5.6)	6.7 (6.9)	0.85 (t, J=6.5Hz, 3H, CH_3); 1.3 (t, J=6.5Hz, 3H, CH_3,); 3.5 (qd, J_{vic}=6.5Hz, J_{gem}=3Hz, 2H, CH_2); 3.4-3.8 (m, 2H, CH_2); 3.9 (s, 1H, CH_3O); 4.7 (s, 1H, CH-SO_2); 6.9 (AB system, J=8Hz, 2H, Aryl H). 7.1 (AB system, J=8Hz, 2H, Aryl H); 7.2-7.7 (m, 5H, Aryl H).
b		167	406.5	59.0 (59.1)	5.5 (5.7)	6.7 (6.9)	1.1 (t, J=7Hz, 3H, CH_3); 1.3 (t, J=7Hz, 3H, CH_3); 2.9-3.1 (m, 2H, CH_2); 3.4-3.6 (m, 2H, CH_2); 3.7 (s, 3H, CH_3O); 5.2 (s, 1H, CH-SO_2); 6.8-7.4 (m, 9H, Aryl H).
c	73	108	300.5	51.9 (52.1)	5.7 (5.4)	9.3 (9.4)	0.8 (t, J=7Hz, 3H, CH_3); 1.3 (t, J=7Hz, 3H, CH_3); 3.0-3.1 (m, 1H,CH_2); 3.1-3.2 (m, 1H, CH_2); 3.5 m, 1H, CH_2); 3.5-3.6 (m, 1H, CH_2); 3.6-3.7 (m, 1H, CH_2); 3.8 (AB system, J=14.5Hz, 1H, CH-SO_2); 4.1 (AB system, J=14.5 Hz, 1H, CH-SO_2); 7.4-7.5 (m, 5H, Aryl H).
d	60	122	314.5	53.4 (53.3)	6.0 (6.0)	8.9 (8.7)	0.8 (t, J=7Hz, 3H, CH_3); 1.3 (t, J=7Hz, 3H, CH_3); 2.4 (s, 3H, CH_3); 2.9-3.3 (m, 2H, CH_2); 3.4-3.7 (m, 2H, CH_2); 3.8 (d, J=14Hz,1H, CH-SO_2); 4.1 (d, J=14Hz, 1H, CH-SO_2); 7.2 (AB system, J=8Hz, 2H, Aryl H); 7.4 (AB system, J=8Hz, 2H, Aryl H).
e	65	203-205	328.5	49.3 (49.5)	5.4 (5.3)	8.8 (8.5)	2.4(s, 3H, CH_3); 3.0-3.6 (m, 4H, $CH_{2morph.}$); 3.7-4.0 (m, 4H, $CH_{2morph.}$); 3.8 (AB system, J=14Hz, 1H, CH-SO_2); 4.2 (AB system, J=14Hz, CH-SO_2); 7.2 (AB system, 2H, J=8Hz, Aryl H); 7.4 (AB system, J=8Hz, 2H, Aryl H).
f	65	102	330.5	50.8 (51.3)	5.7 (5.9)	8.5 (8.6)	0.9 (t, J=6Hz, 3H, CH_3); 1.2 (t, J=6Hz, 3H, CH_3); 3.0-3.3 (m, 2H, CH_2); 3.4-3.7 (m, 2H, CH_2); 3.8 (AB system, J=13Hz, 1H, CH-SO_2); 3.9 (s, 3H, CH_3O); 4.1 (AB system, J=13 Hz,1H, CH-SO_2); 6.9 (AB system, J=8Hz, 2H, Aryl H); 7.4 (AB system, J= 8Hz, 2H, Aryl H).
g	78 [a]	160	404.5	58.5 (58.7)	4.9 (4.9)	7.2 (7.2)	2.4 (s,3H, CH_3); 2.9-4.1 (m, 8H,$CH_{2morph.}$); 4.7 (s, 1H, CH-SO_2); 7.0-7.5 (m, 9H, Aryl H).
h		198	404.6	58.5 (58.6)	4.9 (4.7)	7.2 (7.2)	2.3 (s, 3H, CH_3); 3.0-4.1 (m, 8H, $CH_{2morph.}$); 5.2 (s, 1H, CH-SO_2); 6.8-7.3 (m, 9H, Aryl H).
i	50	156 dec.	342.5	52.5 (55.4)	5.5 (5.8)	8.2 (7.9)	1.1 (m, 6H, $CH_{2pyrrol.}$); 2.9-3.3 (m, 4H, $CH_{2pyrrol.}$); 3.7 (AB system, J=15Hz, 1H, CH-SO_2); 3.8 (s, 3H, CH_3O); 4.1 (AB system, J=15Hz, 1H, CH-SO_2); 6.8 (AB system, J=8Hz, 2H, Aryl H); 7.4 (AB system, J=8Hz, 2H, Aryl H).
l	84	145-147	344.5	48.8 (48.5)	5.0 (5.0)	8.0 (8.1)	3.0-3.8 (m, 8H, $CH_{2morph.}$); 3.8 (s, 3H, CH_3O); 3.9 (AB system, J=14Hz, 1H, CH-so2); 4.1 (AB system, J=14Hz, 1H, CH-SO_2); 6.9 (AB system, J=8Hz, 2H, Aryl H); 7.4 (AB system, J=8Hz, 2H, Aryl H).

a) Total yield of the isolated mixture of the two diastereomers.

Table 10

Analytical and Spectroscopical data for compounds 6

Prod.	Yield %	M.p. °C	M.w.	Calcd.(Found) C	H	N	^{1}H-NMR
a	80	182	370	64.9 (64.5)	5.9 (5.8)	7.4 (7.6)	0.8 (m, 3H, CH_3); 1.4 (m, 3H, CH_3.); 2.9-3.1 (m, 2H, CH_2); 3.4-3.5 (m, 2H, CH_2); 3.8 (s, 3H, CH_3O); 7.0 (AB system, J=7Hz, 2 H, Aryl H); 7.2 (AB system, J= 7Hz, 2H, Aryl H); 7.2-7.4 (m, 6H, Aryl H).
b	75	140	278	60.4 (60.3)	6.5 (6.6)	10.1 (9.9)	0.9 (m, 3H, CH_3); 1.2 (m, 3H, CH_3); 2.4 (s, 3H, CH_3); 3.0-3.2 (m, 2H, CH_2 CH_2); 3.4-3.7 (m, 2H, CH_2); 6.9 (AB system, J=8Hz, 2H, Aryl H); 7.2 (AB system, J=8Hz, 2H, Aryl H); 7.3 (s, 1H, CH-SO_2).
c	80	134	294	55.3 (55.8)	6.4 (6.0)	9.9 (9.5)	0.9 (m, 3H, CH_3); 1.2 (m, 3H, CH_3); 3.0-3.2 (m, 2H, CH_2); 3.5-3.7 (m, 2H, CH_2); 3.8 (s, 3H, CH_3O); 6.9 (AB system, J=8Hz, 2H, Aryl H):7.2 (AB system, J=8Hz, 2H, Aryl H); 7.3 (s, 1H, CH-SO_2).
d	80	180	368	65.2 (65.0)	5.4 (5.3)	7.6 (7.7)	2.4 (s, 3H, CH_3); 2.9-4.0 (m, 8H, $CH_{2morph.}$); 7.0-7.4 (m, 10H, Aryl H).
e	70	185	306	58.2 (58.2)	5.9 (6.1)	9.1 (9.2)	1.2-1.9 (m, 6H, $CH_{2pyrrol.}$); 2.9-3.0 (m, 2H, $CH_{2pyrrol.}$); 3.6-3.8 (m, 2H, $CH_{2pyrrol.}$); 3.8 (s, 3H, CH_3O); 7.0 (AB system, J=9Hz, 2H Aryl H); 7.2 (s, 1H, CH-SO_2); 7.3 (AB system, J=9Hz, 2H, Aryl H).
f	78	167	308	54.5 (54.7)	5.2 (5.3)	9.1 (9.0)	3.1-3.9 (m, 8H, $CH_{2morph.}$); 3.8 (s, 3H, CH_3O); 7.0 (AB system, J=8Hz, 2H, Aryl H); 7.2-7.3 (m, 3H, Aryl H).

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